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ORIGINAL ARTICLE
Prevention and epidemiology

Effect of atorvastatin on muscle symptoms in coronary heart disease patients with self-perceived statin muscle side effects: a randomized, double-blinded crossover trial

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Aims To estimate the effect of atorvastatin on muscle symptom intensity in coronary heart disease (CHD) patients with self-perceived statin-associated muscle symptoms (SAMS) and to determine the relationship to blood levels of atorvastatin and/or metabolites.

Methods and results A randomized multi-centre trial consecutively identified 982 patients with previous or ongoing atorvastatin treatment after a CHD event. Of these, 97 (9.9%) reported SAMS and 77 were randomized to 7-week double-blinded treatment with atorvastatin 40 mg/day and placebo in a crossover design. The primary outcome was the individual mean difference in muscle symptom intensity between the treatment periods, measured by visual-analogue scale (VAS) scores. Atorvastatin did not affect the intensity of muscle symptoms among 71 patients who completed the trial. Mean VAS difference (statin-placebo) was 0.31 (95% CI: -0.24 to 0.86). The proportion with more muscle symptoms during placebo than atorvastatin was 17% ($n = 12$), 55% ($n = 39$) had the same muscle symptom intensity during both treatment periods whereas 28% ($n = 20$) had more symptoms during atorvastatin than placebo (confirmed SAMS). There were no differences in clinical or pharmacogenetic characteristics between these groups. The levels of atorvastatin and/or metabolites did not correlate to muscle symptom intensity among patients with confirmed SAMS (Spearman's rho ≤0.40, for all variables).

Conclusion Re-challenge with high-intensity atorvastatin did not affect the intensity of muscle symptoms in CHD patients with self-perceived SAMS during previous atorvastatin therapy. There was no relationship between muscle symptoms

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and the systemic exposure to atorvastatin and/or its metabolites. The findings encourage an informed discussion to elucidate other causes of muscle complaints and continued statin use.

Keywords Statin-associated muscle symptoms • Coronary heart disease • Atorvastatin • Crossover trial • Placebo-controlled

Introduction

There is firm evidence that statins prevent cardiovascular events, with low rates of serious adverse events.[1–3] Nevertheless, 19% of those using statins for secondary cardiovascular disease prevention in the UK discontinue their treatment within the 1st year, increasing to 26% at 2 years.[4] The principle reason for poor adherence is statin-associated muscle symptoms (SAMS),[5] a heterogeneous group of muscle complaints occurring upon initiation of treatment or an increase in dose.[5] As poor adherence to statin therapy is associated with increased morbidity and mortality,[6] SAMS represent a major challenge in the prevention of cardiovascular disease.

In observational studies, SAMS are frequently reported (10–25%) and statin-treated individuals are more likely to report muscle symptoms than those who are not using a statin.[7–10] In contrast, the randomized trials have not found significant differences in the prevalence of muscle side effects between statin and placebo.[11–13] Strict entry criteria in these trials have been suggested as possible explanations for this discrepancy.[5,14] Patients treated with statins may expect muscle side effects, and therefore report more muscle symptoms than untreated patients, the so-called 'nocebo effect'. Double-blinded crossover trials, exposing participants to both active treatment and placebo in random order, are needed to confirm whether side effects are drug related or not.[2] A small proof-of-concept crossover study[15] and two larger trials designed to test the effect of non-statin therapies[16] and coenzyme Q10[17] in selected patients with SAMS reported conflicting results. Thus, the effect of statin therapy on muscle symptoms remains to be settled.

Although pathophysiological mechanisms[18] and clinical diagnostic algorithms for SAMS have been proposed,[19] it remains unclear how statins produce muscle symptoms, and reliable biomarkers for SAMS are requested.[5] Elevated levels of statin metabolites have been proposed as underlying mechanisms of SAMS.[20] In particular, the lactone metabolites of statins have been associated with muscle toxicity *in vitro* and *in vivo*.[21–23] The relationship between muscle complaints and the exposure to statin metabolites has not previously been studied under randomized, placebo-controlled conditions.

This study aimed to estimate the effect of atorvastatin on muscle symptom intensity in patients with self-perceived SAMS after a coronary heart disease (CHD) event and to determine the relationship between SAMS and the levels of atorvastatin and its metabolites in blood plasma.

Methods

Trial oversight

MUscle Side-Effects of atorvastatin in coronary patients (MUSE) was a multi-centre, randomized, double-blinded, placebo-controlled, two-period crossover trial designed to test the effect of atorvastatin 40 mg/day on muscle symptom intensity.[24] The crossover design allows both within- and between-patient comparisons of muscle symptoms reported on placebo and atorvastatin and requires a lower number of patients than a parallel group design. The protocol is available at ClinicalTrials.gov. There were no significant changes of methods or outcomes after trial commencement. The trial was reported according to the CONSORT guidelines[25] and registered in the European Clinical Trials Database (2018-004261-14) and at ClinicalTrials.gov (NCT03874156), prior to inclusion of the first patient. The trial complies with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics (2018/2302), the Norwegian Medicines Agency (18/17102-16), and the local data protection officers. All patients gave written informed consent. The trial was monitored by research cardiologists.

Participants

All patients discharged with a first or recurrent CHD event between 2016 and 2019 were retrospectively identified through hospital discharge lists from two secondary care hospitals. The catchment area to the hospitals corresponds to 7.4% of the Norwegian population and is representative of Norwegian geography, economy, age distribution, morbidity, and mortality.[26] All patients underwent a standardized telephone interview to reveal whether they had (i) subjective SAMS during ongoing atorvastatin therapy or (ii) previous muscle symptoms that had led to discontinuation of atorvastatin. All patients with self-perceived SAMS were invited to the outpatient clinics for an evaluation of entry criteria and a detailed interview by two study cardiologists before randomization. The interview focused on the temporal association between muscle symptoms and initiation and discontinuation of the statin treatment. Patients who had transitory muscle complaints and who expressed uncertainty as to whether the symptoms were actually caused by the statin, were excluded from the study at baseline (*Figure 1*). An overview of patients excluded prior to the telephone interview is provided in Supplementary material online, *Appendix Figure S1*. The eligibility criteria are described in detail elsewhere.[24] An age and sex-matched control group of CHD patients reporting no history of SAMS despite atorvastatin ≥40 mg, and no other ongoing muscular complaints, was assigned to 7 weeks open-label treatment of atorvastatin 40 mg/day to compare blood plasma concentrations of atorvastatin and metabolites.

Interventions

Participants were randomly assigned by two study cardiologists to atorvastatin in treatment period one, followed by placebo in treatment period two, or vice-versa (AB-BA crossover design). A morning dose of 40 mg/day was chosen, as this is a high-intensity statin treatment frequently used by patients with CHD. Each treatment period was preceded by a 1-week pharmacological washout and lasted for 7 weeks or until intolerable muscle symptoms occurred. The length of the treatment period was chosen on the basis of two observational studies[9,27] indicating that SAMS appear median 2 and 4 weeks after re-challenge and initiation of statin treatment, respectively. The washout periods corresponded to more than 10 half-lives of atorvastatin and its metabolites in the systemic

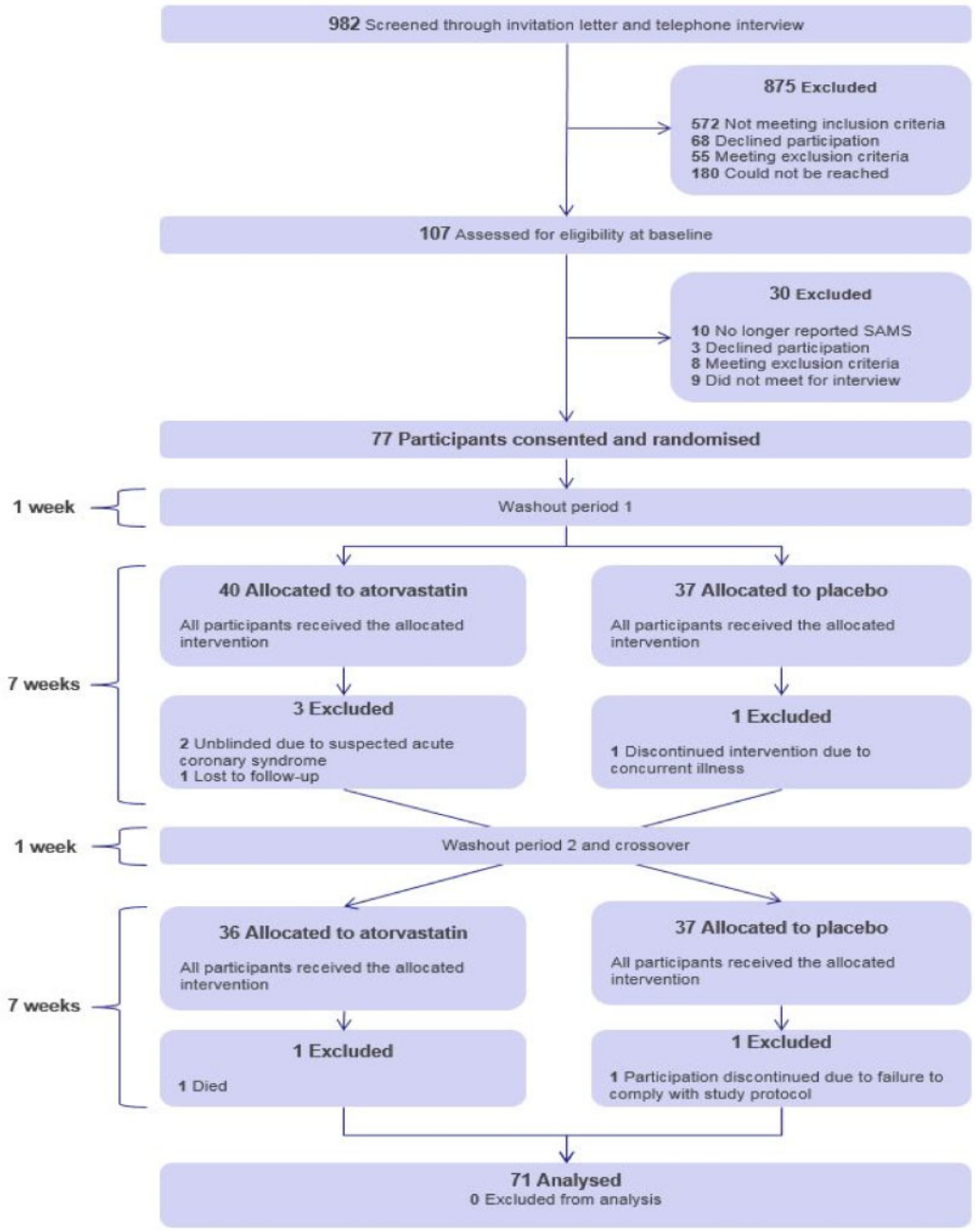

Figure 1 CONSORT flow diagram.

circulation.[28] The primary endpoint was analysed on the basis of symptom intensity in the final 3 weeks of each treatment period. Thus, the risk of carryover effects was minimized as SAMS improve after a median of 2 weeks following treatment discontinuation.[27]

Data collection

Clinical data were collected at baseline from hospital medical records and a self-report questionnaire. Muscle symptom (pain, weakness, tenderness, stiffness, or cramps) intensity was registered weekly in a patient diary using a 0 (no symptoms) to 10 (worst imaginable) visual-analogue scale (VAS). Blood samples for measurement of atorvastatin and metabolites concentration in plasma were obtained immediately prior to the next scheduled dose (C_0, trough concentration) and 2 h after observed tablet intake (C_2, reflecting the peak concentration according to the pharmacokinetic profile of the drug) on the last day of each treatment period. Food intake was allowed prior to collection of C_0 samples but participants fasted until C_2 samples were collected.[28] The blood samples were handled and analysed as previously described.[29] Relevant sequence variants in the *SLCO1B1* (*5, c521T>C, rs4149056), *CYP3A4* (*22,

rs35599367), and *CYP3A5* (*3, rs776746) genes were analysed in baseline blood samples (Light Cycler® 480, Roche Diagnostics). All participants and study personnel were blinded to the results of all laboratory tests including low-density lipoprotein cholesterol and creatine kinase (CK) levels during the study period. Adherence was measured by pill counts in returned containers as well as by drug measurement directly in blood[30] at the end of each treatment period.

Outcomes

The primary outcome was the individual difference in muscle symptom intensity between treatment periods, measured by mean VAS scores during the last 3 weeks of each treatment period. This outcome was chosen to (i) ensure steady-state concentrations of atorvastatin, (ii) maximize the likelihood for the symptoms reported to be truly related to the current (and not previous) treatment period, and (iii) ensure sufficiently long treatment periods for SAMS to appear/disappear. Key secondary outcomes were (i) the proportion with confirmed SAMS, defined as a 25% higher individual mean VAS-score during the treatment period on atorvastatin vs. placebo, and ≥1 cm absolute difference, as this has been regarded as a clinically relevant difference in a validation study of the VAS scale,[31] (ii) the correlation between individual differences in mean muscle symptom intensity and levels of atorvastatin and metabolites among patients with confirmed SAMS, (iii) diagnostic properties of atorvastatin and metabolites for the diagnosis of confirmed SAMS, and (iv) difference between levels of atorvastatin and metabolites in patients with failing placebo test for connecting SAMS to atorvastatin (i.e. non-SAMS) and the control group. Further details on all pre-specified outcomes are available in the statistical analysis plan (SAP) (see Supplementary material online, *Appendix S1*).

Randomization

Participants were randomized by an independent statistician in a 1:1 ratio to a double (i.e. participants, providers, those assessing outcomes) blinded treatment sequence of atorvastatin and matching placebo using an electronic randomization system. Block sizes of four and six in random order, stratified according to centre and previous atorvastatin discontinuation were used. Tablets were encapsulated with identical appearance for atorvastatin and placebo. The containers were collected at the end of each treatment period to avoid participants attempting to compare capsules.

Statistical analyses

Sample size calculations are based on the ability to detect a 1 cm difference in the VAS score between the treatment periods on atorvastatin and placebo.[31] With $n = 68$, we will have 90% power to detect a difference of 1.0 (SD = 2.5) (one-sample *T*-test) and 80% power to detect a difference of 40% SAMS under statins vs. 15% SAMS under placebo (the McNemar test). To account for missing data due to drop-outs or and protocol deviations, we aimed to include 80 patients. All analyses were specified prior to database lock, except where noted, and are described in detail in the SAP. The primary outcome was estimated as the predictive overall margin [95% confidence interval (CI)] of a linear regression model with the difference (atorvastatin minus placebo) as the dependent variable and the stratification factors in the randomization (i.e. centre and previous statin discontinuation) as covariates. The primary analysis was performed on the full analysis set. A secondary analysis was performed on the per-protocol set. A 95% CI for the proportion of confirmed SAMS was estimated with the Wilson score confidence interval.[32] The correlations between differences in muscular symptom intensity and levels of atorvastatin and metabolites among patients with confirmed SAMS were estimated with Spearman rank correlation coefficients, with 95% CIs estimated by the Bonett–Wright approximation.[33] 95% CI of per cent estimates are given in succeeding brackets. Receiver operating characteristics curves and measures of diagnostic accuracy were used to identify cut-off values of metabolite concentrations that can discriminate confirmed SAMS from other muscle symptoms. The comparison of levels of atorvastatin and metabolites between non-SAMS participants and the control group were performed with two-sample *T*-tests with adjustment for unequal variances. A senior statistician, blinded to participants' treatment sequence, performed all analyses using Stata/SE 16.0 (StataCorp LLC, College Station, TX, USA) and Matlab R2014a (The MathWorks, Inc.).

Results

Participant flow, losses, and exclusions are shown in *Figure 1*. Among 982 atorvastatin-treated patients telephoned for assessment of eligibility (82% response rate), 875 were ineligible, most commonly due to no history of self-perceived SAMS. Only one patient had self-perceived SAMS among those who declined to participate. Ninety-seven patients (9.9%) reported SAMS at the baseline interview. Of these, 77 (79%) were randomized in March and August 2019 and 71 completed the trial in June and December 2019. These participants constitute the full analysis set. One patient with significantly elevated blood levels of alanine aminotransferase at the end of the atorvastatin period, and one patient with atorvastatin present in blood plasma during the placebo period were excluded from the full analysis set, leaving 69 participants eligible for the per-protocol analysis of SAMS and atorvastatin exposure. Overall, adherence as measured by pill counts was high with a mean proportion of days covered of 99% (range 91–100%). Adherence was also confirmed by the direct method. There were no missing data on muscle symptom intensity, hospital medical records, or blood samples. Less than 5% of the data from patient questionnaires were missing.

Baseline characteristics

Characteristics were well balanced between treatment sequences (*Table 1*). There was no information in hospital records about previous statin discontinuation (i.e. de-challenge) and repetitive re-challenge tests among study participants. Nineteen patients (27%) had tried ≥2 statins prior to study start. Except for ezetimibe, no other lipid-lowering drugs were used. Baseline muscle symptom intensity was mean 4.6 (SD 2.5) cm. No changes in consumption of analgesics or non-steroidal anti-inflammatory drugs were reported during the trial period. No patients used concomitant treatment with drugs that interact strongly with atorvastatin, coenzyme Q10 or other non-prescription drugs or supplements.

Outcomes

Atorvastatin did not affect the intensity of muscle symptoms (*Figure 2*). In 17% (9.9% to 27%) $n = 12$ patients, more muscle symptoms were reported on placebo than atorvastatin, with mean VAS difference: -3.2 (95% CI -4.3 to -2.2). In 55% (43% to 66%) $n = 39$ patients, no differences in muscle symptom intensity between atorvastatin and placebo was reported, with mean VAS difference of 0.07 (95% CI: -0.14 to 0.28). In 28% (19% to 40%) $n = 20$ patients, more muscle symptoms were reported on atorvastatin than placebo (i.e. confirmed SAMS), with mean VAS difference: 2.9 (95% CI: 2.1 to 3.6).

Table I Baseline characteristics of participants (full analysis set) according to treatment sequence

Characteristic	Atorvastatin → placebo, *N* = 36, (50.7%)	Placebo → atorvastatin, *N* = 35 (49.3%)	Total, *N* = 71
Demographics			
Age (years), mean, (SD)	63.8 (7.8)	63.1 (11.0)	63.5 (9.5)
Female, *N* (%)	12 (33.3)	11 (31.4)	23 (32.4)
Low education,[a] *N* (%)	21 (58.3)	24 (68.6)	45 (63.4)
Non-Caucasian origin, *n* (%)	0 (0)	0 (0)	0 (0)
Index coronary diagnosis			
Myocardial infarction, *N* (%)	30 (83.3)	30 (85.7)	60 (84.5)
Time since last coronary event, months, mean (SD)	25.0 (16.4)	20.4 (10.0)	22.7 (13.7)
Statin treatment and history of intolerance			
Previous atorvastatin discontinuation due to side effects, *N* (%)	13 (36.1)	13 (37.1)	26 (36.6)
Moderate- or low-intensity statin therapy,[b] *n* (%)	19 (52.8)	12 (34.3)	31 (43.7)
No ongoing statin therapy, *N* (%)	5 (13.9)	3 (8.6)	8 (11.3)
Ezetemibe, *N* (%)	10 (27.2)	6 (17.1)	16 (22.5)
Total number of statins used previously, *N* (SD)	1.36 (0.64)	1.31 (0.58)	1.34 (0.61)
Used two different statins previously, *N* (%)	7 (19.4)	7 (20.0)	14 (19.7)
Used three different statins previously, *N* (%)	3 (8.3)	2 (5.7)	5 (7.0)
Cardiovascular risk factors			
Body mass index (kg/m^2), mean, (SD)	29.2 (4.1)	27.3 (4.4)	28.2 (4.4)
Diabetes, *N* (%)	1 (2.8)	4 (11.4)	5 (7.0)
Current smoking, *N* (%)	4 (11.1)	5 (14.3)	9 (13.0)
Low-physical activity,[c] *N* (%)	17 (47.2)	16 (45.7)	33 (46.5)
Laboratory tests			
Creatinine (μmol/L), mean (SD)	80.2 (13.1)	85.1 (33.7)	82.6 (25.5)
Estimated GFR (mL/min/1.73m^2), mean (SD)	79.9 (12.0)	77.5 (16.5)	78.7 (14.3)
Low-density lipoprotein cholesterol (mmol/L), mean (SD)	2.50 (1.19)	2.29 (0.85)	2.40 (1.03)
Creatine kinase (U/L), mean (SD)	136 (99)	146 (94)	141 (96)
Lactate dehydrogenase (mmol/L), mean (SD)	175.4 (28.1)	180.1 (34.7)	177.8 (33.4)
Alanine aminotransferase (U/L), mean (SD)	34.8 (16.5)	35.5 (23.8)	35.1 (20.3)
High-sensitivity C-reactive protein (mg/L), mean (SD)	3.62 (8.08)	2.39 (0.85)	3.01 (6.03)
Comorbidities			
>1 previous coronary event, *N* (%)	10 (27.8)	16 (45.7)	26 (36.6)
Heart failure, *N* (%)	8 (22.2)	6 (17.1)	12 (16.9)
Stroke/transitory ischaemic attack, *N* (%)	2 (5.6)	4 (11.4)	6 (8.5)
Rheumatic or inflammatory disease, *N* (%)	1 (2.8)	0 (0)	1 (1.4)
Arthrosis, *N* (%)	15 (41.7)	10 (32.3)	25 (37.3)
Hypo- or hyperthyroidism, *N* (%)	2 (5.6)	1 (2.9)	3 (4.2)
Anxiety or depression (diagnosis), *N* (%)	6 (16.7)	3 (8.6)	9 (12.7)
Concomitant medication used regularly			
Total number of concomitant drugs, *mean* (SD)	5.3 (2.3)	5.5 (1.9)	5.4 (2.1)
NSAIDs or analgesics, *N* (%)	7 (19.4)	5 (14.3)	12 (16.9)

BMI, body mass index; GFR, glomerular filtration rate; *N*, number; NSAIDS, non-steroidal anti-inflammatory drugs; SD, standard deviation.
[a]Low education was defined by completion of primary and secondary school only.
[b]High-intensity statin therapy means drug regimens that are known to lower low-density lipoprotein cholesterol on average by ~50% (i.e. ≥40 mg atorvastatin/day or ≥20 mg rosuvastatin/day). All the other drug regimens were considered as low- or moderate-intensity statin treatment.
[c]Physical activity <30 min of moderate intensity two to three times weekly.

Irrespective of the treatment sequence, patients reported similar (mean VAS difference 0.28, 95% CI: -0.28 to 0.83) muscle symptom intensities in the two treatment periods. Two patients, both with confirmed SAMS, experienced intolerable muscle symptoms at Week 4 and 5, leading to discontinuation of treatment.

In a *post hoc* analysis, the distribution of patients to the three groups: more muscle symptoms on placebo ($n = 12$), no difference between atorvastatin and placebo ($n = 39$), and more muscle symptoms on atorvastatin ($n = 20$) was not statistically different from 25%/50%/25% ($P = 0.29$; the Pearson χ^2 test for multinomial probabilities).

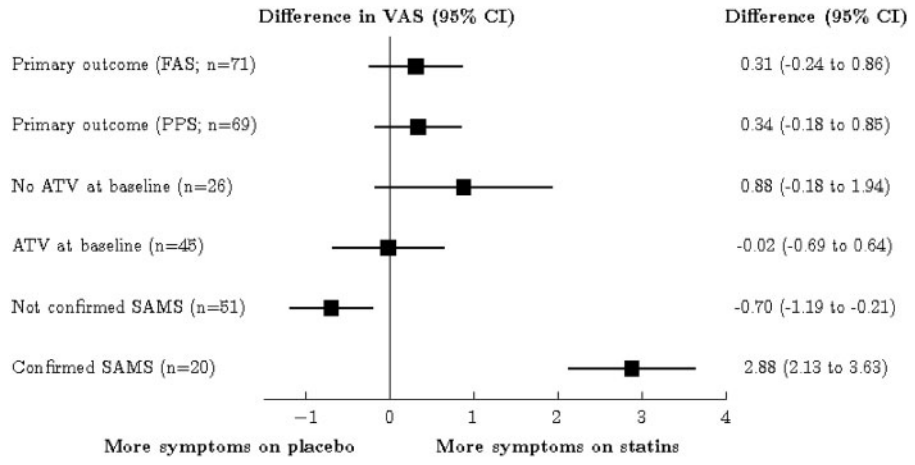

Figure 2 Effect of atorvastatin on muscle symptom intensity in coronary heart disease patients with subjective statin-associated muscle symptoms. ATV, atorvastatin; FAS, full analysis set; PPS, per-protocol set; SAMS, statin-associated muscle symptoms; VAS, visual-analogue scale.

Moreover, when the middle category was excluded, the proportion of patients with more muscle symptoms on atorvastatin was not statistically significantly different from 50% ($P = 0.16$; score test for a single probability). This indicates that the observed distribution of patients to these three groups could be due to chance.

Levels of atorvastatin and/or metabolites in blood plasma did not correlate to the difference between atorvastatin and placebo in muscle symptom intensity among patients with confirmed SAMS (*Table 2*). The individual metabolites and/or sums of metabolites did not discriminate patients with confirmed SAMS from non-SAMS (see Supplementary material online, *Appendix Table S1*). All over, the distributions of metabolite plasma concentrations were comparable between the confirmed SAMS, non-SAMS, and control group patients.

Exploratory comparisons revealed no differences in relevant clinical or pharmacogenetic characteristics between participants with confirmed SAMS and non-SAMS and between the intervention group and the control group without muscle symptoms (*Table 3*). Sixteen out of 19 (84%) patients with self-perceived SAMS on ≥2 statins at study start were classified as non-SAMS.

Table 2 Correlations between the difference in mean muscle symptom intensity and levels of atorvastatin and metabolites among participants with confirmed statin-associated muscle symptoms ($n = 20$)

Drug exposure variable	Spearman's rho (95% CI)
Trough (C0) concentration in nM	
Atorvastatin acid	0.07 (-0.39 to 0.50)
2-OH atorvastatin acid	0.38 (-0.09 to 0.71)
4-OH atorvastatin acid	0.40 (-0.07 to 0.73)
Sum acids	0.31 (-0.16 to 0.67)
Atorvastatin lactone	-0.11 (-0.53 to 0.35)
2-OH atorvastatin lactone	0.27 (-0.20 to 0.64)
4-OH atorvastatin lactone	0.36 (-0.12 to 0.70)
Sum lactones	0.26 (-0.22 to 0.63)
Sum acids and lactones	0.29 (-0.19 to 0.65)
Atorvastatin acylglucuronide	0.11 (-0.35 to 0.53)
Peak (C2) concentration in nM	
Atorvastatin acid	0.07 (-0.38 to 0.50)
2-OH atorvastatin acid	-0.01 (-0.45 to 0.44)
4-OH atorvastatin acid	0.30 (-0.18 to 0.66)
Sum acids	0.10 (-0.36 to 0.52)
Atorvastatin lactone	-0.04 (-0.47 to 0.41)
2-OH atorvastatin lactone	-0.19 (-0.58 to 0.28)
4-OH atorvastatin lactone	0.08 (-0.38 to 0.50)
Sum lactones	-0.17 (-0.57 to 0.29)
Sum acids and lactones	0.01 (-0.43 to 0.45)
Atorvastatin acylglucuronide	-0.08 (-0.50 to 0.38)

C, concentration; CI, confidence interval.

Adverse events

One patient died, most likely due to a primary arrhythmia, and one patient was revascularized due to new-onset angina. Emergency unblinding revealed that both patients received atorvastatin at the time of the adverse event. One patient was un-blinded due to an elevation of alanine aminotransferase >10× upper normal limit at the end of the atorvastatin treatment period, which resolved rapidly when atorvastatin was discontinued. The atorvastatin and metabolites levels in this patient were within the 95% CIs of the mean concentrations in the non-SAMS patients and the control group.

Discussion

In this randomized, double-blinded crossover trial, atorvastatin did not affect the intensity of muscle symptoms among patients with CHD and self-perceived SAMS. The proportion classified with confirmed SAMS (28%), according to our pre-specified definition, is not higher than expected by chance as 17% also reported more symptoms on placebo than on atorvastatin. Although truly

Table 3 Characteristics of participants in the crossover trial and the control group

Characteristic	Confirmed SAMS, *N* = 20 (28.1%)	Non-SAMS, *N* = 51 (71.8%)	Control group, *N* = 40
Baseline characteristics			
Women, *N* (%)	7 (35.0)	16 (31.4)	12 (30.0)
Age (years), mean (SD)	64.1 (11.0)	63.2 (8.9)	64.2 (8.6)
Previous atorvastatin discontinuation, *N* (%)	8 (40.0)	28 (54.9)	0 (0)
High-intensity statin at baseline, *N* (%)	12 (60.0)	28 (54.9)	38 (95.0)
Body mass index (kg/m^2), mean (SD)	27.6 (4.1)	28.5 (4.4)	28.3 (4.1)
High physical activity, *N* (%)	12 (60.0)	27 (54.0)	23 (57.5)
Alanine aminotransferase (U/L), mean (SD)	30.7 (14.9)	36.9 (21.9)	41.6 (23.4)
Creatinine (μmol/L), mean (SD)	84.7 (40.6)	81.9 (16.5)	82.3 (35.6)
Estimated GFR (mL/min/1.73m^2), mean (SD)	78.7 (18.2)	78.5 (12.8)	78.6 (17.4)
Total number of concomitant drugs, *mean* (SD)	5.9 (2.5)	5.2 (1.9)	5.3 (1.6)
Regular use of analgesics, *N* (%)	4 (20.0)	11 (21.6)	3 (7.5)
CYP3A4 *1/*1, *N* (%)	17 (85.0)	47 (92.2)	37 (92.5)
CYP3A4 *1/*22, *N* (%)	3 (15.0)	4 (7.8)	3 (7.5)
CYP3A4 *22/*22, *N* (%)	0 (0)	0 (0)	0 (0)
CYP3A5 *1/*1, *N* (%)	0 (0)	0 (0)	0 (0)
CYP3A5 *1/*3, *N* (%)	3 (15.0)	6 (11.8)	7 (17.5)
CYP3A5 *3/*3, *N* (%)	17 (85.0)	45 (88.2)	33 (82.5)
SLCO1B1 *1/*1, *N* (%)	17 (85.0)	37 (72.6)	26 (65.0)
SLCO1B1 *1/*5, *N* (%)	3 (15.0)	14 (27.5)	13 (32.5)
SLCO1B1 *5/*5, *N* (%)	0 (0)	0 (0)	1 (2.5)
Characteristics during the treatment period on atorvastatin			
Alanine aminotransferase (U/L), mean (SD)	29.9 (14.4)[a]	33.5 (17.1)	45.0 (59.7)
Creatine kinase (U/L), mean (SD)	102 (41.1)	152 (83.6)	128 (77.6)
Lactate dehydrogenase (mmol/L), mean (SD)	165 (35.0)	180 (37.2)	181 (28.3)

C, concentration; CI, confidence interval; SAMS, statin-associated muscle symptom; SD, standard deviation.
[a]One patient with an adverse reaction (i.e. elevation of alanine aminotransferase >10× upper normal limit) at the end of the atorvastatin treatment period was excluded from this analysis.

statin-dependent muscle symptoms are not excluded in a minority of patients, they are likely to be rare compared with the reported prevalence of 10–25%.

MUSE is the first randomized crossover trial designed and powered to determine the effect of statin treatment on muscle symptoms in patients with self-perceived SAMS. The consecutively screened population from routine clinical practice is important for the generalizability of the results. Our prevalence estimate of self-perceived SAMS (10%) was the same as that reported in the large PRIMO survey, exploring the association between high-dose statins and self-reported muscle symptoms in general practice.[9] However, the inherent biases of PRIMO and other observational studies[7,8] limit their ability to evaluate causality.[3]

STOMP[34] was a randomized, blinded trial designed to assess the effect of atorvastatin 80 mg/day on several muscle-related measures in healthy individuals. They reported a small excess of myalgia in statin-treated individuals as compared with placebo (19 vs. 10, $P = 0.05$). The effect of statins on muscle symptoms in the individual patient could, however, not be determined as STOMP was not a crossover study. A two-phase randomized trial (GAUSS-3),[16] enrolling patients with poorly controlled low-density lipoprotein cholesterol levels and history of intolerance to two or more statins, applied a crossover procedure to identify eligible patients for testing the effect of two different non-statin therapies. They found that 43% had muscle symptoms on atorvastatin 20 mg and not on placebo whereas 27% had muscle symptoms on placebo and not on atorvastatin,[16] yielding the same risk ratio of 1.5 as found in our study. However, the results of the crossover phase of GAUSS-3 should be considered suggestive as they were subject to an exploratory analysis without predefined methods in the statistical analysis plan. A similar two-phase crossover trial, investigating the effect of coenzyme Q10 for the treatment of SAMS, found that 36% had muscle symptoms on simvastatin 20 mg and not on placebo as compared with 29% on placebo and not on simvastatin.[17] In contrast to the present study, the Q10 and GAUSS-3 trials were not specifically designed to determine the effect of statins on muscle symptom intensity and potentially eligible participants were not consecutively screened. There was a somewhat lower proportion with statin-dependent muscle symptoms in MUSE (28%) as compared with these trials (42% and 36%). Differences in how muscle symptoms were measured as well as

patient selection of may explain these differences. Eighty-one per cent reported intolerance to three or more statins prior to study start in GAUSS-3, whereas only 7% ($n = 5$) in our study had tried that many statins. Interestingly, all these patients were classified as non-SAMS in our study. Indeed, 16 out of 19 patients with a history of intolerance to ≥2 statins were also classified as non-SAMS. Importantly, atorvastatin did not affect the intensity of muscle symptoms in our primary analysis, and the proportion with confirmed SAMS according to our pre-specified and validated definition was not significantly higher than expected by chance alone. Accordingly, our exploratory analyses revealed no differences in clinical characteristics between patients categorized with confirmed SAMS and non-SAMS. If a subgroup of the patients with statin-dependent muscle symptoms actually exists, the prevalence is likely to be low. The proportion with more symptoms on placebo than atorvastatin may be explained by fluctuations in statin-independent muscle symptoms, alternatively the nocebo effect.[35] Interestingly, a small non-randomized study ($n = 8$) with several crossovers indicates no differences in muscle symptoms between statin and placebo in patients with SAMS.[36]

In this first study, testing also the metabolites of a statin as mediators of SAMS. There was no correlation between muscle symptom intensity and systemic exposure to atorvastatin and its main metabolites. Several *in vitro* studies have reported that lactone metabolites of statins induce toxic effects in muscle.[18] In a previous study, patients were classified with SAMS according to open statin re/de-challenge and their blood levels of atorvastatin metabolites were compared with healthy individuals, both groups using low-dose (10 mg/day) atorvastatin.[21] The blood levels of atorvastatin lactone and 4-OH atorvastatin acid were higher in the SAMS patients.[21] Our placebo-controlled trial demonstrates that the intensity of muscle symptoms is not related to the concentrations of atorvastatin or any of its main metabolites in blood. Moreover, the frequency of sequence variants in CYP3A4/5 and SLCO1B1 was not different between the participants in the randomized trial and the control group without any history of muscle complaints. Potentially, the toxic effects of atorvastatin that occur in the muscle tissue are not adequately reflected by blood plasma concentrations of the drug and metabolites. *In vitro* experiments indicate that influx and efflux transporter proteins are determinants of the local exposure to statin metabolites in skeletal muscle tissue.[37] Consequently, it can be hypothesized that the levels of statin metabolites in muscle tissue are not directly correlated to the exposure in blood. Future studies should obtain muscle biopsies to elucidate further the relationship between muscle symptoms and atorvastatin metabolites and other biomarkers in patients with confirmed SAMS.

Self-perceived SAMS is common (10%) but our conservative estimate of statin-dependent muscle symptoms (<3%) is in line with the estimates of side effects reported in landmark randomized statin trials.[38] Thus, in the clinical perspective, atorvastatin is well tolerated in most patients. A detailed clinical interview elucidating other causes of muscle complaints in these patients appears crucial. Our results may be useful for an informed discussion with patients regarding the likelihood of whether their muscle complaints may be caused by the statin or not. Finally, continuously lowered cholesterol treatment targets together with the emergence of new and expensive lipid-lowering drugs[39] emphasizes the need for optimized use of the cost-effective statins.

Strengths and limitations

The study design enables us to confirm whether the participants' muscle symptoms were truly related to the statin or not, thus addressing the major criticisms of previous SAMS studies.[2] Other strengths include a very low dropout rate, high data quality, and superior adherence to the allocated treatment measured with robust methods.

In all, 802 of 982 patients (82% response rate) responded to the invitation letter and phone calls. Since some of the non-responders may also have experienced SAMS, the prevalence of subjective SAMS in this population could have been slightly higher than the reported estimate. Although observational studies among patients with subjective SAMS[9,27] indicate that the duration of treatment periods should be sufficient for SAMS to appear and disappear in most patients, some participants with perceived changes in muscle symptom intensity after the 8 weeks treatment period may have been incorrectly classified. Even though the time to first noted recovery in muscle symptoms following statin discontinuation was median 2 weeks in a case study of 354 patients with self-perceived SAMS, the time to complete recovery was median 4 weeks.[27] Although it is biologically unlikely that muscle complaints persist for more than 5 weeks after statin discontinuation, the possibility of carryover effects of muscle symptoms in participants with symptoms lasting longer cannot be entirely excluded. To minimize the risk of carryover effects, the outcomes were evaluated only during the last 3 weeks of each test-period of 7 weeks. In addition, the washout periods of 1 week ensured complete pharmacologic clearance of ongoing statin treatment used prior to study start or in the preceding placebo treatment period. Muscle symptoms were registered in a diary that was available for the participants throughout the trial, which could possibly have affected the participants' responses in that previously registered VAS scores may have been used as assessment of symptoms in a subsequent week. The diary was chosen to also allow for participation of elderly patients without access to the internet or mobile phones. Eighty-eight per cent of the present participants who had previously tried 2 or 3 different statins prior to inclusion were classified as non-SAMS by our blinded crossover procedure. Accordingly, reporting side effects after two different statins, or more, does not appear to be a valid marker of true SAMS. Thus, identification of SAMS by the suggested open de-challenge/re-challenge tests[5] remains to be validated and their sensitivity and specificity determined. Such tests are also rarely performed in clinical practice, as none had been performed among the patients screened for the present study. Future studies may establish the validity of both clinical algorithms and screening questionnaires in predicting statin-dependent muscle side effects. Even though atorvastatin is used by the majority of CHD patients, the study results are not outright representative of other statin classes. Moreover, there are regional differences in the distribution of cardiovascular risk factors across Europe, and possibly also in the prevalence and characteristics of the

population with SAMS. Finally, all study participants were Caucasian and the study results should be interpreted accordingly.

Conclusions

Double-blinded re-challenge with high-intensity atorvastatin did not affect the intensity of muscle symptoms in patients with CHD and self-perceived SAMS during previous atorvastatin therapy. There was no relationship between muscle symptoms and the systemic exposure to atorvastatin and/or its metabolites. The findings encourage an informed discussion to elucidate other causes of muscle complaints and continued statin use.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Conflict of interest: O.K. reports having received modest lecture fees from Astra Zeneca, Novartis, and Bayer, outside the submitted work. J.M. reports having received modest lecture fees from Sanofi, Amgen, and Bayer, outside the submitted work. E.G. reports having received modest lecture fees from BMS, Pfizer, Boeringer Ingelheim, and Sanofi, outside the submitted work. L.G. reports having received modest lecture fees from Astra Zeneca, Novo, Amgen, and Sanofi, outside the submitted work. No other disclosures were reported.

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